IPAR

Publicly Available Assessment Report for a Veterinary Medicinal Product

Noropraz, 18.7 mg/g + 140.3 mg/g Oral Paste for Horses

"This product was originally authorised under an EU procedure prior to 1st January 2021 where the UK participated as a Concerned Member State. Therefore, the contents of this Public Assessment Report are not owned by the Veterinary Medicines Directorate. Please contact the original Reference Member State for any queries in relation to this report."

PRODUCT SUMMARY

EU Procedure number	IE/V/0311/001/DC
Name, strength and pharmaceutical form	Noropraz, 18.7 mg/g + 140.3 mg/g Oral Paste for Horses
Active substance(s)	Ivermectin and praziquantel
Applicant	Norbrook Laboratories (Ireland) Limited, Rossmore Industrial Estate, Monaghan, Ireland
Legal basis of application	Generic hybrid application in accordance with Article 13(3) of Directive 2001/82/EC as amended.
Date of completion of procedure	31st July 2013
Target species	Horses
Indication for use	For the treatment of mixed cestode and nematode or arthropod infestations, due to adult and immature roundworms, lungworms, bots and tapeworms in horses: **Nematodes:** Large strongyle:*Strongylus vulgaris* (adult and arterial larvae), *Strongylus edentatus* (adult and L4 tissue larval stages), *Strongylus equinus* (adult), *Tridontophorus* spp. (adult) Small strongyle:Cyathostomum:*Cylicocyclus* spp., *Cylicostephanus* spp.,

	Cylicodontophorus spp., *Gyalocephalus* spp. (adult and non-inhibited mucosal larvae) Parascaris:*Parascaris equorum* (adult and larvae) Oxyuris:*Oxyuris equi* (larvae) Trichostrongylus:*Trichostrongylus axei* (adult) Strongyloides:*Strongyloides westeri* (adult) Habronema:*Habronema* spp. (adult) Onchocerca:*Onchocerca* spp. microfilariae i.e. cutaneous onchocerciasis Lungworm:*Dictyocaulus arnfieldi* (adult and larvae) **Cestodes** (Tapeworm): *Anoplocephala perfoliata* (adult), *Anoplocephala magna* (adult), *Paranoplocephala mamillana* (adult) **Dipteran insects:** *Gasterophilus* spp. (larvae) As tapeworm infestation is unlikely to occur in horses before two months of age, treatment of foals below this age is not considered necessary.
ATCvet code	QP54AA51
Concerned Member States	AT, BE, BG, CY, CZ, DE, DK, EE, EL, ES, FI, FR, HU, IT, LT, LU, LV, MT, NL, NO, PL, PT, RO, SE, SI, SK, UK

PUBLIC ASSESSMENT REPORT

The public assessment report reflects the scientific conclusion reached by the HPRA at the end of the evaluation process and provides a summary of the grounds for approval of the marketing authorisation for the specific veterinary medicinal product. It is made available by the HPRA for information to the public, after the deletion of commercially confidential information. The legal basis for its creation and availability is contained in Article 25.4 of EC Directive 2001/82/EC as amended by Directive 2004/28/EC for veterinary medicinal products. It is a concise document which highlights the main parts of the documentation submitted by

the applicant and the scientific evaluation carried out by the HPRA leading to the approval of the product for marketing in Ireland.

The Summary of Product Characteristics (SPC) for this product is available on the HPRA's website.

I. SCIENTIFIC OVERVIEW

The product is produced and controlled using validated methods and tests, which ensure the consistency of the product released on the market.

It has been shown that the product can be safely used in the target species; the slight reactions observed are indicated in the SPC.

The product is safe for the user, the consumer of foodstuffs from treated animals and for the environment, when used as recommended.Suitable warnings and precautions are indicated in the SPC.

The efficacy of the product was demonstrated according to the claims made in the SPC.
The overall benefit/risk analysis is in favour of granting a marketing authorisation.

II. QUALITY ASPECTS

A. Qualitative and Quantitative Particulars

The product contains the active substances ivermectin (18.7 mg/g) and praziquantel (140.3 mg/g) and the excipients hydroxypropylcellulose, hydrogenated castor oil, titanium dioxide, apple flavour and propylene glycol.
The container/closure system is a plastic dial-a-dose syringe containing 7.49 g of product.The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines.

B. Method of Preparation of the Product

The product is manufactured fully in accordance with the principles of good manufacturing practice at a licensed manufacturing site.
Process validation data on the product have been presented in accordance with the relevant European guidelines.

C. Control of Starting Materials

The active substances are ivermectin and praziquantel, established substances described in the European Pharmacopoeia. The active substances are manufactured in accordance with the principles of good manufacturing practice.
The active substance specifications are considered adequate to control the quality of the materials. Batch analytical data demonstrating compliance with these specifications have been provided.

D. Control on Intermediate Products

Not applicable.

E. Control Tests on the Finished Product

The finished product specification controls the relevant parameters for the pharmaceutical form. The tests in the specification, and their limits, have been justified and are considered appropriate to adequately control the quality of the product.
Satisfactory validation data for the analytical methods have been provided. Batch analytical data from the proposed production site have been provided demonstrating compliance with the specification.

F. Stability

Stability data on the active substances have been provided in accordance with applicable European guidelines, demonstrating the stability of the active substance when stored under the approved conditions.

Stability data on the finished product have been provided in accordance with applicable European guidelines, demonstrating the stability of the product throughout its shelf life when stored under the approved conditions.

G. Other Information

Not applicable.

III SAFETY AND RESIDUES ASSESSMENT (PHARMACO-TOXICOLOGICAL)

This is a generic application according to Article 13(3) – so called generic hybrid application. The reference product cited is Equimax Oral gel for Horses (Virbac Laboratories Ltd.

Results of qualitative and quantitative analysis of the reference product (Equimax Oral Gel) were provided. Based upon the results of these analyses, it could be accepted that the product was essentially similar to the reference product with the exception of the inclusion of the excipient 'Apple Flavour' in the generic formulation.

III.A Safety Testing Pharmacological Studies

The applicant conducted a review of the published literature in support of the pharmacological effects of both ivermectin and praziquantel in the target species.

Ivermectin is a 22,23-dihydro derivative of avermectins B1a and B1b. The mode of action of the avermectins involves an increase in the membrane permeability of chloride ions; in nematodes it activates glutamate-sensitive chloride ion channels.

Praziquantel is an isoquinolone derivative and is a racemate derivative of pyrazinoisoquinoline, and is effective against many species of cestodes and trematodes.

Toxicological Studies

The applicant provided an extensive overview of published literature in support of the toxicological profile of the product

As the product includes the same active substances (ivermectin and praziquantel) at the same concentrations as the reference product (Equimax Oral Gel for Horses), it could be accepted that the toxicological profile of the product will not differ significantly from that of the reference product.

In light of the legal basis of the application (a generic hybrid application) and the composition of the product, no further assessment of the toxicological profile of the product was considered necessary.

User Safety

A user safety assessment was provided. Given the essential similarity of the product with the reference product, it can be accepted that the product will not present any new or greater risk to the user than that of the reference product.
Warnings and precautions as listed on the product literature are adequate to ensure safety to users of the product.

Environmental Risk Assessment

The applicant provided an environmental risk assessment in compliance with the relevant guideline and which included a Phase II assessment for the active substance ivermectin.
It was noted that for the active substance ivermectin, the conclusion of a previous CVMP referral (concerning another product containing ivermectin and administered at the same dose rate to horses) was that no Phase II assessment was required and that no risk mitigation measures were necessary in the SPC of the product.
Consequently, the omission of a phase II ERA for ivermectin and praziquantel (on the basis that none is warranted for ivermectin, praziquantel is considered less ecotoxic than ivermectin and the effects of each active are independent and not additive) was considered acceptable.
It was concluded that the product will not present an unacceptable risk to the environment when used in accordance with the recommendations included in the SPC.

III.B Residues Documentation

Residue Studies

The applicant provided the results of a single time point residue depletion study investigating depletion of ivermectin in the target species.

MRLs

Ivermectin and praziquantel is listed in Table I of the Annex to Commission Regulation (EU) No 37/2010 as follows:

	IVERMECTIN	**PRAZIQUANTEL**
Muscle	-	-
Liver	100 µg/kg	-
Kidney	30 µg/kg	-
Fat/ skin	100 µg/kg	-
Milk	-	-

Withdrawal Periods

Based upon the data provided, it can be accepted that when the product is administered at the recommended treatment dose, a withdrawal period of 35 days is adequate to ensure consumer protection.

The product is not permitted for use in horses producing milk for human consumption.

IV. CLINICAL ASSESSMENT

This is a generic application according to Article 13.3 of Directive 2001/82/EC, as amended.

The applicant provided results of a study conducted to investigate bioequivalence of the product with the reference product for the active substance ivermectin. Bioequivalence to the reference product was not demonstrated in accordance with guideline requirements for the parameter AUC for the active substance ivermectin.

In light of the findings of the *in-vivo* bioequivalence study, the applicant provided results of comparative analyses (including qualitative/quantitative composition, particle size, viscosity and *in-vitro* dissolution) of test and reference products in order to support pharmaceutical (and therefore therapeutic) equivalence of the product with the reference product.

Based upon the *in vitro* data provided, pharmaceutical (and therefore therapeutic) equivalence of the two formulations could be accepted.

IV.APre-Clinical Studies Tolerance in the Target Species of Animals

The applicant conducted a target animal safety study in horses. Based upon the findings of this study, it can be accepted that the product was well tolerated when administered at a dose of up to 3 x RTD for three consecutive days.

Resistance

The product formulation is qualitatively and quantitatively identical to the reference product formulation in terms of the active substances ivermectin and praziquantel. The proposed conditions of use are identical for both products. As such, the risk of resistance development is not expected to differ between the two products.

Adequate warnings and precautions are included in the product literature.

IV.B Clinical Studies Laboratory Trials Field Trials

As the comparative bioavailability study only investigated bioequivalence with the reference product for the active substance ivermectin, the applicant provided the results of a negatively controlled dose confirmation study investigating efficacy of the product (praziquantel component) against the helminth *Anoplocephala pefoliata*.

In addition, the applicant conducted an extensive search of the published literature in order to support the proposed indications. Based upon the totality of data presented (pharmaceutical equivalence (with exception of flavouring), clinical efficacy study and bibliography), the proposed indication against adult cestodes was considered to have been adequately supported.

V. OVERALL CONCLUSION AND BENEFIT/RISK ASSESSMENT

The data submitted in the dossier demonstrate that when the product is used in accordance with the Summary of Product Characteristics, the benefit/risk profile for the target species is favourable and the quality and safety of the product for humans and the environment is acceptable.

VI. POST-AUTHORISATION ASSESSMENTS

The SPC and package leaflet may be updated to include new information on the quality, safety and efficacy of the veterinary medicinal product. The current SPC is available on the HPRA website.

This section contains information on significant changes which have been made after the original procedure which are important for the quality, safety or efficacy of the product.

Changes:
None.